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Der Inhalt dieser Schrift weicht von den am Anmeldetag eingereichten Unterlagen ab

(54) Verfahren zum Verschluß von Gefäßmißbildungen, insbesondere von zerebralen Aneurysmen, unter Verwendung von drahtförmigen Embolisationselementen

(57) Bei einem Verfahren zum Verschluß von Gefäßmißbildungen, insbesondere von zerebralen Aneurysmen, unter Verwendung von drahtförmigen Embolisationselementen, die mittels eines Führungskatheters an den Ort der Gefäßmißbildung plaziert werden und dort aufgrund einer mechanisch/thermischen Vorbehandlung eine vorgegebene, die Thrombogenität und/oder Zellproliferation fördernde geometrische Struktur annehmen, wird zur weiteren Verbesserung der Behandlung von Gefäßmißbildungen vorgeschlagen, die Embolisationselemente derart auszuführen, daß sie nach Passieren des Führungskatheters eine komplex geformte, dreidimensionale Struktur einnehmen mit einer Enveloppe, die in etwa der anatomischen Struktur der zu behandelnden Gefäßmißbildung entspricht und/oder daß die Embolisationselemente mit einer biologisch aktiven Beschichtung versehen werden.

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Description

The invention concerns a method to seal vascular malformations, especially cerebral aneurysms, using wire-like embolization elements that are placed at the location of the vascular malformation using a guide catheter where they assume a set geometric structure that promotes thrombogenicity and/or cell proliferation and is determined by mechanical and thermal pretreatment.

In the majority of cases, spontaneous subarachnoidal hemorrhaging is caused by the rupture of an aneurysm of the basal cerebral vessels. In addition to intensive medical care, the aneurysm must be eliminated which has nearly always been accomplished by open neurosurgery. Increasingly, however, endovascular treatments are gaining in importance as less invasive alternatives that may be equally successful. The same holds true for the treatment of arteriovenous vascular malformations. The most promising technique among endovascular methods is to seal vessels with metal coils that are guided within a guide catheter and placed at the location of the vascular malformation where they assume a set geometric structure determined by mechanical and thermal pretreatment, and are released by a mechanical, thermal or electrochemical mechanism. There is neither clinical long-term experience with this method, however, nor are there any comprehensive experimental and histopathological studies. Until now, the assumption was that the embolization coils needed to be highly thrombogenic to provide reliable occlusion. Various manufacturers attempted this by using various metals as the basic substance (such as platinum, iridium or tungsten) The utilized metals were required to be highly inert, thrombogenic and strongly radiopaque. One attempted to increase thrombogenicity by incorporating plastic fibers in the spirals (nylon, Dacron) (WO 95/25480-A1). Clinical experience, however, confirms that neither method yields a sufficient seal. Clinical experiments are increasingly indicating that the long-term results are unsatisfactory due to the frequently observed recanalization of the underlying vascular dilation. The method must be substantially improved before it can become established as a routine surgery and alternative to conventional methods. With the exception of the cerebral area, the same holds true for all other induction areas for such

embolization coils (such as the peripheral vascular region).

One cause of recidivism is the compacting of the coils that, due to their preset shape (helical spirals), tend to contract and assume a different shape supported by the pulsation of the arterial blood flow. This disadvantage can only be partially compensated by introducing several coils into the aneurysm sac to produce a very high packing density. However, this is technically often unfeasible or can only be done at great risk to the patient. There exists the increased danger of perforation of the vascular wall and dislocation of individual coils in the lumen of the carrier vessel. Experimental results have illustrated that only an extremely high packing density can ensure histologically stable occlusion.

The main reason for recidivism is not the insufficient thrombogenicity of the embolization coils, but rather the spontaneous premature fibrinolysis that dissolves within one to two weeks the thrombus that nearly always arises after application of the coils.

On the other hand, another problem is that the high thrombogenicity causes the clots to migrate from the aneurysm into the carrier vessel and produce secondary embolic complications (strokes within the cerebral area).

In summary, the prior-art methods have the following disadvantages:

1. A tendency to compact resulting in recidivism
2. The required high packing density that increases the risk of treatment and greatly increases the cost of therapy.
3. Risk of secondary complications from an embolism.

The present invention is based on the problem of developing a method of the initially-cited type to minimize the danger of secondary embolisms in the treatment of the vascular malformations, especially cerebral aneurysms, and to prevent spontaneous fibrinolysis and yield a stable, lasting occlusion and, if possible, the repair of the existing

defect of the vascular wall.

This problem is solved using a method of the initially-cited type whereby the guide catheter is inserted, and the embolization element assumes a complex three-dimensional structure with an envelope that approximately corresponds to the anatomical structure of the vascular malformation to be treated, and/or the embolization elements are provided with a biologically active coating.

The method according to the invention avoids the disadvantages associated with the state of the art and provides long-term elimination of the cited vascular malformations. In addition to treating aneurysms of the basal cerebral vessels, the method is suitable for sealing blood vessels that lead to tumors, for treating vascular shunts between the lung and heart that will not close in newborns (angiomas, patent ductus arteriosus), and the occlusion of fistulas and shunts between veins and arteries.

Based on the predetermined geometric structure according to the invention of the utilized embolization elements with an envelope that approximately corresponds to the anatomical structure of the vascular malformation to be treated, a dense wire network results that fills the entire inner area of the malformation as an even foundation and framework for the newly forming tissue. This substantially improves both thrombogenicity and cell proliferation. By means of the invention, an embolization element approximating the anatomical structure of the vascular malformation is introduced into the malformation. It does not contract or becomes deformed, and it prevents recanalization resulting from changes in hemodynamics (the wave breaker effect). As with conventional coils, the embolization element is applied stretched through a conventional microcatheter. After the preformed embolization element is inserted, it assumes the predetermined complex shape determined by its intrinsic elasticity (memory effect) and occludes the aneurysm or restricts blood flow until an intraluminal thrombus arises from the slower flow and turbulence in the lumen. In contrast to previously used helical coils, the predetermined structure prevents the element from reorganizing and resuming a helical shape, and it also prevents the recanalization of the aneurysm's

interior. Since multiple helical embolization coils no longer have to be introduced, the risk of perforation is clearly reduced The application time and hence the patient's exposure to x-rays are reduced, as well as the danger of individual coils becoming dislocated.

In the method according to the invention, a thrombus is induced, and the growth of fibroblasts and other connective tissue cells is stimulated to allow the overgrowth of the former ostium. The shape of the embolization element is selected such that compacting is avoided. In the final analysis, it is only this that ensures the definitive repair of the defects. The length of the wire coil can vary from approximately 2 to 100 cm, typically 5 to 20 cm, (depending on the size of the vascular malformation to be treated), and it is shaped by being wound around a template or a winding base and by selectively shaping it, e.g. by means of controlled heating of the metal. The sizes of the templates can differ so that the various complexly shaped embolization elements can be available in different sizes (envelope diameter of 2 mm to 20 mm or more). The diameter of the coils is 0.1 to 0.4 mm to permit application using conventional vascular coaxial microcatheters. The diameter of the base wire is 0.01 to 0.05 mm.

In surgeries using the device, the anatomical structure of the vascular malformation is first measured in an x-ray, and then the suitable embolization element is selected from the various different sizes.

It has been shown that embolization elements that form a cervical, conical or elliptical envelope structure are most suitable in the majority of cases.

It is suitable to use an embolization element whose network structure is such that the spacing between neighboring wire sections within the embolization element is < 1.5 of the wire diameter.

The thrombogenicity and cell proliferation can be further increased by means of the method according to the invention when a biologically active coating is used on the

embolization elements.

Such a biological coating causes the binding and/or release of biologically active substances that promote cell growth for the formation of a stable vascular occlusion. The biologically active substances accelerate the initial colonization of the embolization elements with cells (fibroblasts), promote their proliferation over the embolization elements, and promote cell growth. Furthermore, thrombogenic substances are envisioned that reinforce the formation of long-lasting clots in the cavity and prevent acute fibrinolysis. The cavity is accordingly completely filled, which is a prerequisite for the occlusion of the ostium with endothelial cells and for the permanent repair of the defect.

Biologically active substances according to the invention are in particular fibronectin, vibronectin, laminin, albumin, collagens, growth hormones such as insulin or somatropin, growth factors such as insulin-like growth factors (IGF-I, IGF-II), epidermal growth factor (EGF), thrombocyte growth factor (PDGF), fibroplast growth factor (bFGF, aFGF), transforming growth factor (TGF-beta), erythropoietin, nerve growth factors, brain cell growth factors or endothelial cell growth factors (VEGF), tumor necrosis factors (TNF-alpha, TNF-beta), prostatropins, prostaglandins, thromboxans, leucotriens, immunoglobulins, interferons, interleukins, and/or thrombus-promoting substances such as thrombin, fibrinogen, coagulation factors or prothrombin. However, it is preferable to use proliferation-promoting substances such as fibronectin.

It has proven to be particularly advantageous when, according to another feature of the invention, and intermediate layer consisting of polymers is applied to the embolization elements as a carrier material for the biologically active substances. The biologically active substances are covalently bonded to functional groups on the polymer surface by means of bivalent bridge molecules (spacers). For example, diisocyanates, dicarboxylic acid chlorides, dicarboxylic acid succinimides, other dicarboxylic acid derivatives or carbodiimides can be used as spacers.

According to another feature of the invention, the biologically active substances can also

be incorporated in a degenerating polymer layer, e.g. consisting of polylactides, polyesters or polyamino acids. They are then continuously released with the progressive decomposition of the polymer layer.

The preferred intermediate polymer layer according to the invention is substituted poly-p-xylylene that is created by CVD polymerization (CVD: chemical vapor deposition) of for example amino, hydroxy, carboxy, (hydroxyl)alkylene, chlorine or trifluoroacetyl-p-cyclophanes according to the Gorham process. The p-cyclophanes are split under a low pressure and at temperatures > 650°C, and polymerized at temperatures below 200°C on the surface of the embolization element. This method has numerous advantages in regard to the application according to the invention such as the even coating from the gas phase, the lack of solvents, polymerization initiators or additives, the effective use of the available quantities of monomers, and the ability to specifically adjust surface parameters.

In addition, the intermediate polymer layer can be applied by plasma polymerization of olefins along with functional groups suitable for bonding biologically active substances such as allyl amine, allyl alcohol, butenols, butyl amines, acrylic acid, acrylic acid derivatives, acrylates, and hydroxymethyl acrylates. In addition, ethene, propene, ethyne, propyne, acetone - typically mixed with oxygen or sulfur dioxide - are suitable for creating such an intermediate polymer layer.

Furthermore, it has been shown that the intermediate polymer layer can also be created by coating the embolization elements with polymers such as polyurethanes, polyolefins, polyesters or polysaccharides from a liquid phase. The intermediate polymer layer is then activated by means of an argon plasma treatment. By subsequently irradiating the activated surface with an excimer lamp or an excimer laser, graft copolymers can be created with hydrogels such as polyhydroxymethyl acrylate, polyacrylate, polyethylene oxide, or poly-4-(acryloyloxy)butyl hydrogen glutarate. The biologically active substances are bonded to the terminal functional groups.

According to the invention, a polymer thread instead of an embolization coil made of metal can be used that, for example, can be made of polytetrafluoroethylenes, polyamides, polyesters, polyolefins, polyurethanes or polycarbonates, and radiopaque substances are typically added such as powdered tantalum, powdered tungsten, barium sulfate, and bismuth oxide, carbonate or sulfate. In this instance, the functional groups suitable for bonding bioactive substances - to the extent they are not already present on the surface of the intermediate polymer layer - can be generated by applying one of the cited functionalized polymer layers, or by using an established method to create functional polymer groups such as plasma etching, the radiation or wet chemical modifications.

Additional explanations of the method according to the invention can be found in the schematically represented exemplary embodiment in Fig. 1 to 3.

Fig. 1 to 3 illustrate the treatment of a cerebral aneurysm. In Fig. 1, a guide catheter (1) for an embolization element (2) is guided and monitored using X-rays into the damaged blood vessel (3) into the interior of the aneurysm (4). Then the wire-like embolization element (2) is advanced in the guide catheter into the area of the malformation. An embolization element (2) consists of a metal or a metal alloy that is free from surface oxidation at room and body temperature or while being heated or cooled such as platinum or a platinum/iridium alloys. However, embodiments of other metals or alloys consisting for example of tungsten, tantalum, iridium, gold, niobium, rhodium, osmium, palladium, nickel/titanium alloys, or stainless steels are also possible.

The embolization element (2)/(5) is mechanically and thermally pretreated (memory effect) so that it assumes a predetermined three-dimensional geometric structure after passing through the guide catheter with an envelope that approximately corresponds to the anatomical structure of the vascular malformation to be treated (see Fig. 2 and 3).

The three-dimensional network (5) arising in this manner that evenly fills the vascular malformation substantially promotes cell growth and hence substantially contributes to

the desired rapid and stable occlusion of the aneurysm. The desired result is enhanced much further by additionally providing the embolization element (2)/(5) according to the invention with a biologically active coating.

In addition to the cited advantages, coating the embolization element also reduces friction resistance when inserting the stretched embolization element (2) through the guide catheter (1) which makes surgery substantially easier. Of course, the application of a biologically active coating consisting of an intermediate polymer layer and biologically active substances is not restricted to the geometry of the embolization element. Conventional embolization elements can also be activated by means of the suggested biologically active coating with similar success.

Patent Claims

1. Wire-like embolization elements to seal vascular malformations, especially cerebral aneurysms, that assume a predetermined geometric structure determined by mechanical and thermal pretreatment that promotes thrombogenicity and/or cell proliferation, characterized in that the embolization element assumes a complexly-shaped, three-dimensional structure with an envelope that approximately corresponds to the anatomical structure of the vascular malformation to be treated, and/or the embolization element is provided with a biologically active coating.

2 Embolization element according to claim 1, characterized into the envelope is in the shape of a sphere, cone or ellipsoid.

3. Embolization element according to one of claims 1 or 2, characterized in that the spacing between neighboring wire sections within the net-like, three-dimensional wire structure is < 1 5 of the wire diameter at every location.

4. Embolization element according to one of claims 1 to 3, characterized in that a polymer layer is applied to the surface of the embolization element as a carrier material for the biologically active substances.

5. Embolization element according to one of claims 1 to 4, characterized in that the biologically active substances are bonded to the polymer via spacer molecules that react with functional groups on the intermediate polymer layer.

6. An embolization element according to one of claims 1 to 4, characterized in that the polymer layer is biodegradable, and the biologically active substances are incorporated in the polymer layer.

7. Embolization element according to one of claims 1 to 5, characterized in that the intermediate polymer layer is created by CVD polymerization.

8 Embolization element according to one of claims 1 to 5, characterized in that the intermediate polymer layer is created by plasma polymerization.

9. Embolization element according to one of claims 1 to 6, characterized in that the intermediate polymer layer is applied from a liquid phase, and the functional groups are created by subsequent graft polymerization.

10. Embolization element according to one of claims 1 to 9, characterized in that the entire embolization element is made of polymers.

11. Embolization element according to claim 10, characterized in that the embolization element is doped with radiopaque substances.

Attached. one-page of drawings

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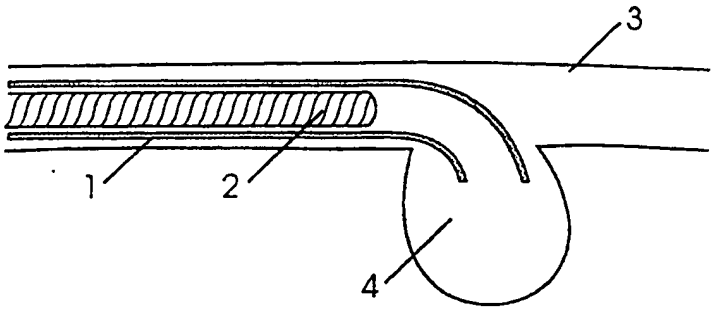
Abb.1



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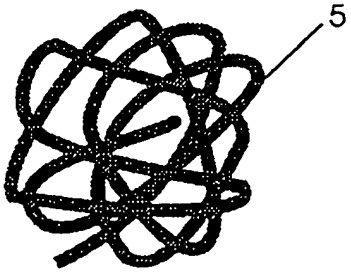

1 Mikrokatether

2 Kugelspirale, gestreckt

3 Blutgefäß

4 Mißbildung (Aneurysma)

5 Kugelspirale in entspannter Form (Endzustand)

→ Richtung des Blutstroms

Abb.3